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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/699,243	MARKL ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8,10-13 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8,10-13 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed February 8, 2007. Currently, claims 1, 4, 7-8, 10-13, 15-19 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the Claims, applicants' arguments.

3. This action is FINAL.

4. This action contains new grounds of rejection necessitated by amendment.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4, 7-8, 10-13, 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to "a contiguous CpG island sequence that comprise SEQ ID NO: 36 or 37".

The specification describes sequencing 103 "novel" sequences. The specification fails to teach the chromosomal location, the gene, or the cDNA of these

DNA sequence fragments. The specification fails to describe contiguous CpG islands of SEQ ID NO: 34-37.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of specifies have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly,

Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

The claims encompass "a contiguous CpG island sequences that comprise SEQ ID NO: 36 or 37." For illustration purposes, the following embodiment is encompassed within the scope of the claims but fails to be described.

**********(SEQ ID NO 36) ******** (CpG) *********.

Here, this CpG region is encompasses within the same larger CpG island as SEQ ID NO: 36 and is contiguous with SEQ ID NO: 36. However, the flanking or context sequence of "CpG" has not been disclosed or described. No precise definition, such as by structure, formula, chemical name, or physical properties has been provided. The specification appears to merely provide a wish or plan for obtaining the claimed chemical invention which does not constitute description of the subject matter.

Similar to Example 7 of the Written Description guidelines, the specification teaches a fragment of a cDNA or genomic DNA, but does not provide the full cDNA or genomic DNA.

Response to Arguments

The response traverses the rejection. The response asserts that the claims are supported by a "formula, physical properties and structure sufficient to describe contiguous CpG islands of SEQ ID NO: 36-37" (see page 7 of response filed August 15, 2005). The response points to page 5, 8 of the specification indicating the "formula" for the contiguous CpG islands. The claims are notably directed to contiguous CpG islands

(see Claim 1, for example). The response asserts that the specification teaches a formula; namely, "a CpG island sequence associated with a particular SEQ ID NO sequence of the present invention is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CPG dinucleotides corresponding to an Observed/Expected Ratio >0.6), and a GC Content >0.5." This argument has been thoroughly reviewed, but is not found persuasive because the "formula" provided does not provide what the nucleotide structure of the coordinately methylated contiguous CpG island sequences are. The description may provide how to obtain the sequences, but not what they are. The response further asserts that physical properties and structure are also implicit within this definition, because the definition absolutely requires that the associated sequence is contiguous with the portion of the CpG island. Applicants contend, therefore, that the relevant sequences are sufficiently described because of the formula and requirement for physical linkage along the chromosome, because a person of ordinary skill in the art would be able to determine, without undue experimentation what these sequences are, based on applicant originally filed disclosure." This argument has been thoroughly reviewed, but is not found persuasive because whether a person of ordinary skill in the art could determine what the sequences are does not provide that the sequences were described in the instant specification. While this may provide enablement with the considerations of undue and experimentation, written description is a separate issue. With the exception of SEQ ID NO: 36 and 37, referred to above, the skilled artisan cannot envision the detailed

chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Fevel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Here, the specification has provided no sequences that are methylated contiguous CpG island sequences for SEQ ID NO: 36, 37. The response illustrates numerous examples of CpG regions encompassed by the claims. However, the claims require looking at a CpG diunucleotide from within the "island". The specification, nor the claims, describe this CpG dinucleotide outside of SEQ ID NO: 36 or 37. The claims are broadly drawn to CpG dinucleotides outside of SEQ ID NO: 36 or 37 and do not rely on the nucleotide sequence of SEQ ID NO: 36 or 37.

The response asserts that for public policy reasons, applicants are entitled to claims that are commensurate in scope not only with what applicants have specifically described and exemplified and with that which one of skill could obtain. This argument has been thoroughly reviewed but deemed not persuasive. The description requires that applicants provide a description of their invention and in this case would encompass a description of the structure (i.e. sequence) of the contiguous sequences.

The response asserts that the claimed sequences are not like those of EST sequences, however provides no arguments to support the assertion. Much like the EST example in the Written Description guidelines, applicants have provided a partial structure and are claiming a much larger structure.

Therefore, only nucleic acids of SEQ ID NO: 36, 37, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4, 7-8, 10-13, 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to performing a methylation assay on DNA to determine the methylation state of "a CpG dinucleotide" as indicative of diagnosis or prognosis of breast cancer, for example. The instant specification teaches hypermethylation refers to the methylation state corresponding to an increased presence of 5-mCyt at one or a plurality of CpG dinucleotides within a DNA sequence of a test DNA sample relative to the amount of 5-m-Cyt found at corresponding CpG dinucleotides within a normal control DNA sample.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5,552,277; 5,846,712; 5,856,094).

In CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8

behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1).

Pao et al. (Human Molecular Genetics, Vol. 10, No. 9, pages 903-910) teaches the EDNRB promoter displays heterogeneous site specific methylation patterns in normal and tumor cells. Pao analyzed 11 individual CpG sites located throughout the CpG island. The sites showed that specific sites with high methylation levels in several tumors are also methylation in normal tissues suggesting they might serve as foci for further de novo methylation (abstract). Figure 2 illustrates the methylation profile in the promoter in primary tissue samples. The data on the 11 individual CpG sites spanning the whole island demonstrated that several non-adjacent CpG sites showed high methylation in tumor tissues and some of the normal samples (page 904, col. 1). Pao teaches that increased methylation is found at CpG-130 the 5' most CpG dinucleotide analyzed which is located on the fringe of the CpG island (page 905, col. 1). Pao teaches CpG 336 remained resistant to hypermethylation even when adjacent CpGs were highly methylated. Moreover Pao teaches that the findings showed that in the EDNRB 5' regulatory region, prostate, bladder and colon normal tissues have methylation patterns that are particular to each type of tissue (page 906, col. 1). Some sites within the CpG island appeared to be preferential targets for de novo methylation whereas others seemed to be protected from hypermethylation changes (page 906, col.1). Thus, the teachings of Pao suggest that analysis of a single dinucleotide would not allow predictable association absent further experimentation to determine the methylation pattern in the particular tissue types and in normal tissues. The individual

sites in a particular island are not predictably associated with each other dinucleotide in the island. Moreover, normal tissues may show methylation at particular sites.

Cameron et al. (Blood, vol. 94, No. 7, pages 2445-2451, October 1999) teaches the p15 CpG island methylation is heterogeneous. An analysis of the p15 CpG island illustrates that there was marked heterogeneity for the specific CpG sites methylated (abstract). Cameron teaches that the density of methylation within the CpG island and not any specific location correlates between with transcriptional loss (abstract). Cameron teaches that he importance of hypermethylation at 1 or 2 CpG sites and their location relative to transcription start sites remain to be determined (page 2445, col. 1). Thus, Cameron does not support the argument that a single dinucleotide may be representative of the entire CpG island. In fact Cameron teaches that the exact location of methylated sites varied not only between samples but also between alleles from each cancer (page 2447, col. 2).

Guidance in the Specification.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof.

Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6). The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. The specification has not taught that a predictable correlation exists between nucleic acids which are "contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37". The specification has not described any "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37", therefore, it is unpredictable that "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" are indicative of cancers absent unpredictable and undue experimentation. The

skilled artisan would first be required to determine "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer. Moreover, the art does not support the idea that all contiguous CpG islands are associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner.

As noted by Pao, it is not clear that the presence of hypermethylation of a single CpG is indicative of a disorder. Pao and Cameron teach individual sites are not sufficient to assess disease state. Pao further teaches certain normal tissues show some methylation. Thus, the presence of a hypermethylated CpG is not representative of breast cancer, for example. Moreover, the claims are not specifically drawn to hypermethylation compared to normals. The art does not support that the methylation state of a CpG dinucleotide in SEQ ID NO: 36 is not representative of the state of the CpG dinucleotides in the CpG island. The skilled artisan would be required to perform

additional experimentation which is unpredictable and undue to determine which CpG island dinucleotides are individually associated with diagnostics. The art, namely Pao and Cameron both support the heterogeneity of individual CpG site methylation.

Neither the art nor the specification support the assertion that a CpG dinucleotide may allow diagnostic or prognostic assays for cancer. Similarly, the specification and the art do not support that a contiguous CpG island sequence that comprises SEQ ID NO: 36 would be similarly methylated.

Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 or single dinucleotides are associated with cancer. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches not all dinucleotides are representative of the methylation over the sequence and normal sequences contain some normally methylated dinucleotides to diagnosis cancer based upon dinucleotides. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Moreover, the declaration filed by applicants indicates a hypermethylation. The declaration is not directed to particular dinucleotides. Thus, the results showed in the declaration are not commensurate in scope with the claimed invention. Thus given the broad claims in an

art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been adequately enabled. In responding to the examiner's rejection, applicants have set forth several reasons for traversal which will be addressed in the order argued.

First, the affidavit under 37 CFR 1.132 filed May 23, 2003 is insufficient to overcome the rejection of claims 1-2, 4, 7-12 based upon enablement as set forth in the last Office action. The declaration filed by Dr. Cathy Lofton-Day of May 23, 2003 has been thoroughly reviewed, but found not persuasive to enable the full scope of the instant claims. Moreover, the declaration filed by applicants indicates a hypermethylation. The declaration is not directed to particular dinucleotides. Thus, the results showed in the declaration are not commensurate in scope with the claimed invention.

The declaration is drawn to SEQ ID NO: 36 and 37. The claims encompass "continuous" and SEQ ID NO: 36, 37, for example. Based upon the unpredictability discussed above, there is no evidence of record to suggest that a contiguous CpG

island sequences that comprise SEQ ID NO: 36 are associated with breast cancer. Neither the specification, the declaration or the art provide any evidence of a correlation between a contiguous CpG island sequences that comprise SEQ ID NO: 36 with breast cancer. Moreover, the data is silent with respect to CpG islands which are "a contiguous CpG island sequences that comprise SEQ ID NO: 36." It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." The instant showing is not commensurate in scope with the claims, as there is no evidence that a contiguous CpG island sequences that comprise SEQ ID NO: 36 are associated with breast cancer, for example.

Finally, the response traverses the rejection with respect to the "a contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" within the scope of the claims. The specification teaches that the CpG island sequence associated with the sequence of a particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence and satisfies the criteria of having both a frequency of CpG diunucleotides corresponding to an Observed/Expected Ration >0.6, and a GC content >0.5 (page 3, lines 24-28). This argument has been reviewed but is not convincing because the specification has not provided a representative number of associated sequences that comprise SEQ ID NO: 36-37. The specification has not provided a larger portion of a CpG island. Therefore, detecting an associated sequence has not been taught in the specification. Moreover, the art does

not support the idea that contiguous CpG island sequences that comprise SEQ ID NO: 36 are associated with cancer of prostate, colon or breast. The art of Pao and Cameron support the position that dinucleotides are hetergenously methylated. Finally, the declaration filed is not commensurate in scope with the instant claims. The declaration filed is directed to SEQ ID NO: 36 and 37. There is no showing of any additional sequences. It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 are associated with cancer. The response asserts that the claims have been amended to encompass "only those contiguous CpG island that would also correlate with the same respective cancer(s)." This argument has been thoroughly considered and not found persuasive because to determine which sequences are "contiguous CpG island sequences that comprise SE QID NO:36" would require unpredictable and undue experimentation. As discussed at length above, p156 and EDNRB are very specific example of contiguous regions within the same CpG island which do not share hypermethylation. To determine which regions are and which regions are not associated with cancer requires further undue and unpredictable experimentation. The specification does not provide any guidance in determining which sequences are "continuous" without performing the further unpredictable and undue experimentation.

The response asserts that a CpG island that is continuous with a CpG island of SEQ ID NO: 36, 37 would be easily isolatable and methylation state of one or more

CpG residues relative to a control could be done with little experimentation. This argument has been thoroughly reviewed, but is not found persuasive because, even if the contiguous CpG island sequences could be determined, it is unpredictable which sequences would and which sequence would not be methylated as indicative of cancer. As discussed at length above, Pao and Cameron, provides a detailed analysis of a particular gene and various regions within the gene illustrating that the gene is not predictably methylated, as suggested by the response.

Second, it is agreed that Toyota teaches examples were CpG islands act independently. However, Toyota, as pointed out by the response does teach diffierent subregions within a given CpG island such as regions 5-7 of island 2. Toyota specifically teaches that regions 5, 6,7 behaved quite differently than did regions 1-3. Methylation of these regions was less frequent than in regions 1 and 2: 22 of 36 cell lines had no detectable methylation there, despite often showing methion of region 1 and 2. However, when methylation was present (in 13 of 36 cell lines), it affected all three regions simultaneously, although to varying extents. This illustrates that the different dinucleotides within at least one DNA sequence that of an island do not necessarily share coordination in their methylation patterns (;age 4538, col. 1). Moreover, Toyota specifically teaches that regions 3, 4, and 8 correspond to the edge of the CpG islands and behave a little differently than the hearts of the CpG islands (page 4538, col. 1). Thus, it is clear that the response is asserting that the instant SEQ IDN O: 36 and 37 are partial islands and may contain additional sequences on either side. However, it is unclear how far down the genome each island may stretch. Further it is

unclear where the edge of the islands lie and whether these CpG sites behave a little differently than the hearts of the CpG island. It is unclear whether SEQ ID NO: 36 an 37 are in the heart of the island or whether they are on the edge. Thus, it is not predictable that all CpG dinucleotides within the claimed regions would behave in similar manners as argued by the response.

Third, the response asserts that Pao, which teaches that not all CpGs in a CpG island were hypermethylated even when adjacent to CpGs that were hypermethylated does not run counter to applicants recitation of coordinately methated CpGs. The response asserts that the claims do not require that all CpGs within a CpG island are coordinately methylated but rather only that the mehtylation change of those CpGs is a coordinate change. This argument has been reviewed but is not persuasive. The claims state that the "state of a CpG dinucleotide" is determined and the prognosis or diagnosis is determined by the detection of hypermethylation. It is unpredictable which CpG sites may be used for analysis and which sites do not provide any guidance to the diagnosis or prognosis.

Fourth, as discussed about for Pao, since there is heterogeneity across a CpG region, the skilled artisan would be unable to assay for a single CpG dinucleotide and provide a diagnosis or prognosis for breast cancer, for example. Even, applicant's own work, as set forth in the declaration filed in 2003 illustrates analysis over a larger region.

Finally, the response provides a declaration by Dr. Kurt Berlin. The declaration filed by Dr. Kurt Berlin, February 8, 2007 has been thoroughly reviewed. It is noted that Dr. Kurt Berlin's declaration appears to be directed to SEQ ID NO: 46 and 47. The

instant claims are drawn to SEQ ID NO: 36 and 37. Thus, it is not clear how the declaration speaks to the instant claims.

The response asserts that the declaration describes a paper further confirming as was appreciated in the art at the time of filing that there is a significant correlation for co-methylation within CpG regions. It is noted that the paper filed by the response and declaration was available approximately 6 years after the filing of the instant application. Moreover, the paper cited, specifically states that "our data suggest DNA methylation to be ontogenetically more stable than previously thought." Which further suggested that this paper may show data which moves away from previously understood mechanisms. Thus, it is not clear that at the time the invention was made, namely 2000, the art appreciated any correlation for comethylation within CpG dense regions.

Moreover, the data illustrated in the Eckhardt reference appears to be a profiling of normal human chromosomes and does not appear to be directed at differential methylation upon cancer progression or occurrence. Thus, it is not clear that the cited article is directed to diagnostic or prognostic analysis.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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